from the blood into the brain. This process takes about 11 seconds.[27] When consumed in smokeless tobacco, nicotine is absorbed through the lining of the mouth into the bloodstream and flows to the brain.

Once inside the human brain, nicotine binds to unique receptors on the surfaces of brain cells. These nicotinic receptors normally interact with a natural chemical messenger called acetylcholine, but can also be stimulated by nicotine to alter mood, alertness, and cognition. Exposure to nicotine causes the number of nicotinic receptors on the surfaces of brain cells to increase[28] and significantly alters the brain's normal electrical and metabolic activity.[29] Nicotine's actions on the central nervous system produce both

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[27] Department of Health and Human Services, Office on Smoking and Health, *The Health Consequences of Smoking: Nicotine Addiction, a Report of the Surgeon General* (Jul. 29, 1988), DHHS Publication No. (CDC) 88-8406 (Washington DC: GPO, 1988), at 13-14 (hereinafter cited as Surgeon General's Report, 1988). *See* AR (Vol. 129 Ref. 1592).

Benowitz NL, *Clinical Pharmacology of Inhaled Drugs of Abuse: Implications in Understanding Nicotine Dependence*, NIDA Research Monograph 99 (Rockville MD: National Institute on Drug Abuse, 1990), at 17. *See* AR (Vol. 3 Ref. 18).

[28] Benwell MEM, Balfour DJK, Anderson JM, Evidence that tobacco smoking increases the density of (–)-[^{3}H]nicotine binding sites in human brain, *Journal of Neurochemistry* 1988;50:1243-1247. *See* AR (Vol. 136 Ref. 1570).

[29] Surgeon General's Report, 1988, at 79-123. *See* AR (Vol. 129 Ref. 1592).

sedating and stimulating effects, depending on dose and circumstances.[30] Nicotine also plays a role in weight regulation.[31]

In addition to its sedating and stimulating effects, nicotine causes and sustains addiction. Nicotine directly affects an intrinsic brain system, known as the mesolimbic system, that signals pleasure and reward and modulates emotions. When stimulated by an addictive substance, the mesolimbic system responds by rewarding the repeated consumption of the substance.[32] It is widely believed that amphetamine, cocaine, and nicotine all cause the compulsive drug-seeking behavior of drug addiction through the same mechanism: increasing the activity of the neurotransmitter dopamine within the mesolimbic system.[33]

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[30] Pritchard WS, Gilbert DG, Duke DW, Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity, *Psychopharmacology* 1993;113:95-102. *See* AR (Vol. 3 Ref. 23-1).

Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 105 Ref. 965).

Norton R, Brown K, Howard R, Smoking, nicotine dose and the lateralisation of electrocortical activity, *Psychopharmacology* 1992;108:473-479. *See* AR (Vol. 3 Ref. 22).

Golding JF, Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving, *Pharmacology, Biochemistry and Behavior* 1988;29:23-32. *See* AR (Vol. 3 Ref. 23-3).

[31] Surgeon General's Report, 1988, at 431-432. *See* AR (Vol. 129 Ref. 1592).

[32] Pomerleau OF, Pomerleau CS, Neuroregulators and the reinforcement of smoking: towards a biobehavioral explanation, *Neuroscience and Biobehavioral Reviews* 1984;8:503-513. *See* AR (Vol. 3 Ref. 20-1).

Wise RA, Rompre PP, Brain dopamine and reward, *Annual Review of Psychology* 1989;40:191-225. *See* AR (Vol. 3 Ref. 19-1).

Clarke PBS, Mesolimbic dopamine activation—the key to nicotine reinforcement? *CIBA Foundation Symposium* 1990;152:153-168. *See* AR (Vol. 3 Ref. 19-2).

[33] *Id.*

Pontieri FE, Tanda G, Orzi F, *et al.*, Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs, *Nature* 1996;382:255-257. *See* AR (Vol. 711 Ref. 51).

Extensive scientific evidence demonstrating the significant effects of nicotine in tobacco products on the structure and function of the body is discussed in detail in the remainder of this section. The magnitude and wide dissemination of the scientific evidence demonstrates that it is foreseeable to a reasonable person in the position of tobacco manufacturer that many consumers will use tobacco products for these pharmacological effects.

3. Nicotine Is Widely Recognized as Addictive, and It Is Foreseeable That Consumers Will Use Cigarettes and Smokeless Tobacco To Satisfy an Addiction

Nicotine's effects on the brain are the biological basis of nicotine addiction—an addiction that has been proven by a wealth of laboratory and epidemiological evidence and recognized by every major independent medical organization that has studied the question. Nicotine's widely recognized addictive properties make it foreseeable to any reasonable person that a substantial proportion of users of tobacco products will consume these products to satisfy their addiction.[34]

a. Scientific Consensus

Overwhelming scientific evidence and broad recognition that nicotine is an

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Di Chiara G, Imperato A, Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats, *Proceedings of the National Academy of Sciences of the United States of America* 1988;85:5274-5278. *See* AR (Vol. 66 Ref. 26).

Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine, *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

[34] FDA's conclusion that the pharmacological effects and uses of nicotine in cigarettes and smokeless tobacco are foreseeable rests on published literature, including widely disseminated government reports. FDA's conclusion that the tobacco industry knows that nicotine has substantial pharmacological effects and that consumers use tobacco for these effects, *see* section II.C., below, is based largely on internal company documents.

addictive, dependence-producing substance emerged in the 1980's.[35] All leading expert and public health organizations in the United States and the international community with expertise in tobacco or drug addiction now recognize that nicotine is addictive. The first major organization to do so was the American Psychiatric Association in 1980, when its *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III), defined the Tobacco Dependence Disorder and the Tobacco Withdrawal Syndrome.[36] Since 1980, nicotine in tobacco products has also been recognized as addictive by the U.S. Surgeon General (1986 and 1988)[37]American Psychological Association (1988),[38] the Royal Society of Canada (1989),[39] the World Health Organization (WHO) (1992),[40] the

[35] The terms "addictive" and "dependence-producing" are used interchangeably among experts and scientific organizations and generally refer to the persistent and repetitive intake of a psychoactive substance despite evidence of harm and a desire to quit. In this document, FDA also uses both terms interchangeably. The term "abuse liability" also refers to a substance's ability to produce dependence or addiction.

[36] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 3d ed. (Washington DC: American Psychiatric Association, 1987), at 159-160, 176-178. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[37] Department of Health and Human Services, Office on Smoking and Health, The Health Consequences of Using Smokeless Tobacco, A Report of the Advisory Committee to the Surgeon General (Apr. 1986), NIH Publication No. 86-2874 (Bethesda, MD:1986). *See* AR (Vol. 128 Ref. 1591)

Surgeon General's Report, 1988. *See* AR (Vol. 129 Ref. 1592).

[38] *Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce*, U.S. House of Representatives, 100th Cong., 1st Sess. 1 (Jul. 29, 1988) (statement of the American Psychological Association). *See* AR (Vol. 5 Ref. 43-5).

[39] Royal Society of Canada, *Tobacco, Nicotine, and Addiction: A Committee Report*, prepared at the request of the Royal Society of Canada for the Health Protection Branch, Health and Welfare Canada (Aug. 31, 1989), at v-vi. *See* AR (Vol. 62 Ref. 814).

[40] WHO, *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (Geneva: World Health Organization, 1992), at 76. *See* AR (Vol. 43 Ref. 175).

American Medical Association (1993),[41] and the Medical Research Council in the United Kingdom (1994).[42] Every expert organization that has commented on whether nicotine is addictive has concluded that it is.

Recognition of nicotine addiction is now so universal that even the vast majority of scientists who have received funding from the tobacco industry believe that nicotine is addictive. In a survey of principal investigators of research projects funded by the tobacco industry in 1989, 83.3% agreed strongly and an additional 15.3% agreed somewhat that cigarette smoking is addictive.[43] Moreover, as demonstrated in section II.C., below, the tobacco industry itself, despite public pronouncements to the contrary, has long known nicotine to be addictive.

Salient findings that reflect nicotine's addictiveness include the following:

Epidemiological Evidence.

- Persons who have smoked at least one cigarette are about twice as likely to develop dependence as are persons who have ever tried cocaine or alcohol.[44]

[41] American Medical Association, Ethyl alcohol and nicotine as addictive drugs, in *1993 AMA Policy Compendium* (Chicago: AMA, 1993), at 35. *See* AR (Vol. 37 Ref. 2).

[42] Medical Research Council, *The Basis of Drug Dependence*, MRC Field Review (London: Medical Research Council, 1994), at 11. *See* AR (Vol. 41 Ref. 105).

[43] Cummings KM, Sciandra R, Gingrass A, *et al.*, What scientists funded by the tobacco industry believe about the hazards of cigarette smoking, *American Journal of Public Health*, 1991;81(7):894-896. *See* AR (Vol. 5 Ref. 44).

[44] Anthony JC, Warner LA, Kessler RC, Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey, *Experimental and Clinical Psychopharmacology* 1994;2:244-268. *See* AR (Vol. 37 Ref. 4).

- More than half of people presenting for treatment of alcohol or drug abuse who also smoke cigarettes report that quitting smoking would be harder than giving up their other drug of abuse.[45]
- Despite the interest of 70% of smokers in quitting smoking, fewer than 3% succeed per year.[46]
- About two of every five users of smokeless tobacco have attempted to quit and failed,[47] and 68% of smokeless tobacco users who have attempted to quit report an average of four such attempts.[48]
- About 50% of smokers recovering from surgery for a smoking-related disease (e.g., lung cancer) and whose prognosis and symptoms would be improved by abstinence resume smoking.[49]

Evidence from Animal and Human Laboratory Studies.

- Nicotine has been determined to have significant potential to produce addiction in humans on the basis of the same screening tests used to evaluate the addictive potential of any drug by the World Health Organization, the Drug Enforcement Administration,

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[45] Kozlowski LT, Wilkinson A, Skinner W, *et al.*, Comparing tobacco cigarette dependence with other drug dependencies, *Journal of the American Medical Association* 1989;261(6):898-901. *See* AR (Vol. 41 Ref. 92).

[46] Centers for Disease Control and Prevention, Cigarette smoking among adults—United States, 1993, *Morbidity and Mortality Weekly Report* 1994 (Dec. 23);43:925-930. *See* AR (Vol. 36 Ref. 616-1).

[47] Novotny TE, Pierce JP, Fiore MC, *et al.*, Smokeless tobacco use in the United States: the adult use of tobacco surveys, *Monographs/National Cancer Institute* 1989;8:25-28. *See* AR (Vol. 41 Ref. 109).

[48] Severson HH, Enough snuff: ST cessation from the behavioral, clinical, and public health perspectives, in *Smokeless Tobacco or Health, An International Perspective,* Smoking and Tobacco Control Monograph 2, NIH Publication No. 93-3461 (Washington DC: DHHS, 1993), at 281-282. *See* AR (Vol. 18 Ref. 5-1).

[49] Surgeon General's Report, 1988, at 150. *See* AR (Vol. 129 Ref. 1592).

the National Institute on Drug Abuse (NIDA), the College on Problems of Drug Dependence, pharmaceutical companies, and FDA's Drug Abuse Advisory Committee (the Committee).[50] *See* section II.A.3.c.i., below.

- Nicotine's effects in the brain have been shown to be critical in the self-administration of nicotine by both animals and humans.[51] (The tendency of a substance to be self-administered demonstrates its ability to cause an animal or human to seek repeated doses of the substance.) This finding is a key element of addiction.
- The ability of nicotine to produce strong physiological and behavioral effects, including death at high doses, is no less than that of amphetamine or morphine.[52]

Other Biological Evidence.

- Nicotine increases dopamine activity in the mesolimbic system of the brain. As with cocaine, amphetamine, and other drugs, this effect is believed to contribute to the compulsive drug-seeking behavior of addiction.[53]
- Chronic nicotine exposure causes the number of nicotinic receptors on the surfaces of brain cells to increase. This phenomenon is associated with tolerance to the effects of nicotine and has been well documented in animals and people.[54]

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[50] *Id.* at 270.

[51] *Id.* at 166, 173-175, 182-192.

Corrigall WA, Coen KM, Nicotine maintains robust self-administration in rats on a limited access schedule, *Psychopharmacology* 1989;99:473-478. *See* AR (Vol. 136 Ref. 1561).

[52] Surgeon General's Report, 1988, at 272-274, 594. *See* AR (Vol. 129 Ref. 1592).

[53] Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine, *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

[54] Marks MJ, Burch JB, Collins AC, Effects of chronic nicotine infusion on tolerance development and nicotine receptors, *Journal of Pharmacology and Experimental Therapeutics* 1983;226:817-825. *See* AR (Vol. 41 Ref. 103).

II.A.3.

Commercial Evidence.

- Non–nicotine-containing tobacco products have never proved successful substitutes for tobacco despite the sophistication of some of them (e.g., Philip Morris' Next) in mimicking the non–nicotine-mediated effects of conventional cigarettes.

These data are just a few selections from the overwhelming evidence that has led the world's health authorities to classify nicotine as addictive. The following sections describe in detail the definition of addiction and how the widely known scientific evidence would lead any reasonable manufacturer to foresee that a significant proportion of tobacco consumers will become addicted to nicotine and will use tobacco products to satisfy their addiction.

b. Definition of Addiction

The tobacco industry is virtually alone in publicly contending that nicotine is not addictive. Its primary argument for rejecting the massive body of research and the expert opinion of every authoritative medical organization that has considered the issue is to claim that the entire scientific community is using the wrong definition of addiction.[55] According to the tobacco industry, the "traditional criteria" of addiction are "meaningful

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Surgeon General's Report, 1988, at 53-54. *See* AR (Vol. 129 Ref. 1592).

Benwell MEM, Balfour DJK, Anderson JM, Evidence that tobacco smoking increases the density of (–)-[^{3}H]nicotine binding sites in human brain, *Journal of Neurochemistry* 1988;50:1243-1247. *See* AR (Vol. 136 Ref. 1570).

[55] The tobacco industry cites the opinions of several physicians and scientists to support the contention that nicotine is not addictive. In most cases, as described below, the opinions have been taken out of context, and the cited individuals are on record as believing that nicotine is addictive. Those individuals who agree with the industry that nicotine is not addictive comprise a "handful of scientific supporters." Hwang SL, Ono Y, Tobacco dream team: experts who insist nicotine isn't addictive, *Wall Street Journal* (Mar. 23, 1995). *See* AR (Vol. 711 Ref. 29).

intoxication, withdrawal, and tolerance." Although withdrawal and tolerance are still considered criteria for addiction, "intoxication" has not been considered a necessary criterion for over thirty years. The industry cites no medical dictionary, expert panel, or scientific organization for this specific definition; the "criteria" are instead extracted from portions of a definition developed in the 1950's and used by the editors of the 1964 Surgeon General's Report on tobacco.[56] This definition was premised on the now-discarded, early twentieth-century conception of drug addiction as a personality disorder characterized by weakness of will, immaturity of character development, and immorality.[57]

Within months of publication of the Surgeon General's Report in 1964, its definition of addiction was cast aside by the scientific community. In a major report, the World Health Organization (WHO) recognized that intoxication was not a distinguishing characteristic of dependence for any drug under its purview.[58] Indeed, people dependent on stable daily doses of opiates may display no observable signs of intoxication.[59] Conversely, it is widely known that nonaddicting drugs such as antihistamines and atropine and scopolamine preparations can produce intoxication.[60] Moreover, under the

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[56] Department of Health, Education, and Welfare, Public Health Service, *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service* (Washington DC: GPO, 1964), at 349-352. *See* AR (Vol. 43 Ref. 156).

[57] Surgeon General's Report, 1988, at 248. *See* AR (Vol. 129 Ref. 1592).

[58] WHO Expert Committee on Addiction-Producing Drugs, *WHO 1964,* World Health Organization Technical Report Series No. 273, Thirteenth Report (Geneva: World Health Organization, 1964), at 3-20. *See* AR (Vol. 43 Ref. 169).

[59] Surgeon General's Report, 1988, at 251. *See* AR (Vol. 129 Ref. 1592).

[60] Garrison JC, Histamine, bradykinin, 5-hydroxytryptamine, and their antagonists, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* 8th ed. (New York: Pergamon Press, 1990), chap. 23, at 584, 586. *See* AR (Vol. 711 Ref. 14).

old definition, cocaine and amphetamines would not clearly have been considered addictive because of lack of evidence at the time demonstrating physical dependence.[61] The scientific community thus rejected the old definition of addiction because of new scientific insights about the nature of addiction, more than 15 years before finding nicotine to be addictive.

Today, drug addiction has been defined by scientific organizations from both laboratory and clinical perspectives. The laboratory perspective assesses experimentally whether a substance alters the central nervous system in a manner that can produce characteristic addictive behavior in humans.

While the laboratory perspective focuses on the chemical substance, the clinical perspective on drug addiction assesses whether an individual in society consumes the substance in a manner that demonstrates addiction. Consensus clinical criteria for diagnosing addiction have been developed by the American Psychiatric Association and were most recently published in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) in 1994:

> Criteria for Substance Dependence
>
> A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:
>
> (1) tolerance, as defined by either of the following:

Brown JH, Atropine, scopalomine, and related antimuscarinic drugs, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* 8th ed. (New York: Pergamon Press, 1990), chap. 8, at 157. *See* AR (Vol. 711 Ref. 14).

[61] WHO Expert Committee on Addiction-Producing Drugs, *WHO 1964,* World Health Organization Technical Report Series No. 273, Thirteenth Report (Geneva: World Health Organization, 1964), at 3-20. *See* AR (Vol. 43 Ref. 169).